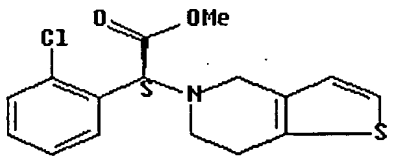
New crystalline forms of clopidogrel hydrobromide and methods of their preparation

Technical Field

The invention concerns new crystalline forms of the hydrobromide of the (alpha S) alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester (thereinafter clopidogrel hydrobromide), which are characterized by X-ray (RTG) diffraction and infrared spectra, and methods of their preparation.

Background Art

The (alpha S) alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester, clopidogrel of formula I



I

is an anti-thrombic agent that was described in CZ patent 274 420 (EP 281 459), wherein blood coagulation decreasing activities of various salts of this substance were also demonstrated. Currently sold clopidogrel-based pharmaceutical formulations contain this active agent in the form of its hydrogensulfate salt (HSO_4^- anion). The method of preparation of the S-enantiomer published in the above-cited patent involves reaction of the racemic mixture with optically active camphorsulfonic acid and subsequent separation of the diastereoisomer.

The respective salt of clopidogrel with camphorsulfonic acid is converted, by a solution of sodium hydrogen carbonate in methylene chloride medium, into an optically active base, which is obtained by evaporation of the solvent.

The evaporation residue of the active base is converted into the respective salt. Specifically, the hydrobromide is obtained by dissolving the base in diethyl or diisopropyl ether and precipitating drop by drop with 48% hydrobromic acid. Drying the formed precipitate affords crystals with the melting point of 111 °C.

In the cited patent, toxicity of the hydrobromide is also evaluated, which is even somewhat lower than that of the currently used hydrogensulfate. (LD_{50} of clopidogrel hydrogen sulfate is 2591 mg and LD_{50} of clopidogrel hydrobromide is 4268 mg).

Disclosure of Invention

The new crystalline Form I of clopidogrel hydrobromide is characterized by interplanar distances ascertained by X-ray diffraction, d: 4.01 Å; 4.39 Å and 3.17 Å, or by infrared spectrogram with bands at 1743; 1421; 1237, 760 and 728 cm^{-1}.

The new crystalline Form II of clopidogrel hydrobromide is characterized by interplanar distances ascertained by X-ray diffraction, d: 4.52 Å; 3.83 Å; 3.48 Å, or by infrared spectrogram with bands at 1754; 1436; 1317 and 1223 cm^{-1}.

The new crystalline form III of clopidogrel hydrobromide is characterized by the following peaks ascertained by X-ray diffraction at 2θ positions: 7.796 °; 15.380 °; 18.389 °; 19.369 ° and 23.895 °.

The crystalline Form I can be obtained from a solution of the base in toluene by precipitating with 48% hydrobromic acid. This procedure yields first an oily emulsion of the hydrobromide in toluene, which is, however, with further stirring converted into a crystalline matter. Stirring can be performed at room temperature but it is also possible to decrease the temperature gradually.

A preferable method of preparation of crystalline form I involves adding a 48% solution of hydrobromic acid in water to a solution of 5 to 15% of the clopidogrel base in toluene, whereas the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.5.

Form II can be obtained by reaction of a solution of the clopidogrel base in an organic solvent, e.g. ethyl acetate or toluene, with a solution of hydrobromic acid in toluene. Crystalline Form II gradually matures at decreased temperature, i.e. precipitation is performed preferably at temperatures 0 to 30 °C and crystals grow preferably at temperatures lower than 10 °C. The method preferably involves using a solution of the clopidogrel base having a concentration 5 to 40 weight % and precipitating it with a solution of hydrogen bromide in toluene of concentrations 5 to 15 weight %, whereas the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.1.

Alternatively, Form II can be obtained by introducing gaseous hydrogen bromide into a solution of clopidogrel base in an organic solvent, preferably in an aromatic C_6-C_{12} hydrocarbon, for example toluene. Preferably, hydrogen bromide is introduced at a lowered temperature, e.g., -15 °C to 30 °C, more preferably at a temperature lower than 10 °C; at this temperature, in a stirred solution, the crystalline Form II further matures. Usual time of stirring is 2 to 8 hours. A preferable concentration of the solution of the clopidogrel base is 15 to 40 weight % and the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.1.

Form III can be prepared by a similar method, wherein, however, hydrogen bromide is introduced into a solution of clopidogrel having a concentration lower than 15 %, preferably 1 to 10 %. Hydrogen bromide is again introduced at a lowered temperature, for example -15 °C to 30 °C. Form III matures at a lower temperature by stirring for 2 to 8 hours.

Form III can be used as an intermediate which is further processed into the pharmaceutically applicable Form II. This can be made by crystallization or precipitating an alcoholic solution of clopidogrel hydrobromide. Alcohols for said solution are selected from the series of C_1-C_5; 2-propanol being preferred. Another less polar solvent can be added to the solution, preferably an ether, ester or ketone. Methyl *tert*-butyl ether has turned out to be especially preferred. In this manner, Form II can be obtained in an especially high purity.

Melting points of all the forms are difficult to reproduce and identification fails. They range between about 113 and 145 °C.

Brief Description of Drawings

Figure 1 shows infrared spectra of clopidogrel hydrobromide Form I.

Figure 2 shows infrared spectra of clopidogrel hydrobromide Form II.

Figure 3 shows an X-ray diffraction pattern of clopidogrel hydrobromide Form I.

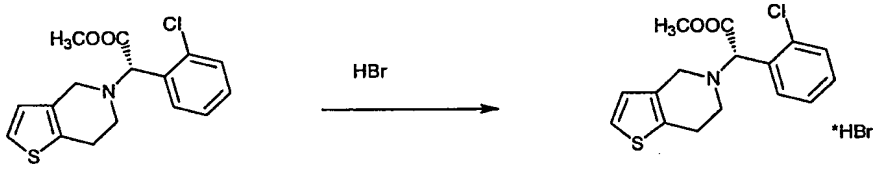
Figure 4 shows an X-ray diffraction pattern of clopidogrel hydrobromide Form II.

Figure 5 shows an X-ray diffraction pattern of clopidogrel hydrobromide Form III.

Examples

The invention is elucidated by the following examples, which have purely illustrative character and do not limit the extent of the invention in any respect.

Scheme



(I) (II)

Example 1

3.38 g (0.0105 mol) of the clopidogrel base of formula (I) are dissolved in 10 ml of toluene at room temperature. A solution of HBr in toluene (11.5 ml of the solution containing 0.86 g of HBr) is added at once under stirring. The resulting precipitate is stirred at room temperature for 1 hour. After this time, the reaction mixture is left sitting at temperature +6 °C for 4 hours. The precipitate is sucked off and washed with toluene. After air drying, 2.9 g of yellowish crystals of hydrobromide of formula (II) (69%) are obtained, having the melting point 132 to 138 °C. The crystals were characterized by an X-ray diffraction pattern and infrared spectra as the crystalline Form II (Figure 2).

The results of the X-ray diffraction were converted into interplanetary distances D:

2θ[deg]	d [Å]	I	I/I0
11.20	9.1631	141.00	20.84
11.45	8.9654	149.01	22.02
12.20	8.416	92.29	13.64
13.30	7.7222	71.52	10.57
15.10	6.8096	137.52	20.32
16.11	6.3826	161.60	23.88
17.58	5.8541	88.96	13.15
18.84	5.4651	78.63	11.62
19.75	5.2163	145.54	21.51
22.82	4.522	676.62	100.00
24.41	4.2313	261.39	38.63
25.50	4.0526	104.53	15.45
26.97	3.8363	422.01	62.37
29.20	3.5489	217.39	32.13
29.74	3.4851	289.33	42.76
32.08	3.2375	168.90	24.96
33.61	3.0935	163.74	24.20
37.76	2.7644	175.01	25.87

Example 2

6.1 g (0.0189 mol) of the clopidogrel base of formula (I) are dissolved in 60 ml ethyl acetate at room temperature. The solution is cooled down in a water-ice bath to temperature +5 °C and 20.8 ml of solution of HBr in toluene is added drop by drop within 0.5 hours at this temperature. The mixture of crystals in toluene is stirred for another 2 hours at temperature 0 to +5 °C. The resulting crystalline fraction is sucked off and washed with ethyl acetate. After air drying, 3.7 g of cream-coloured crystals of the hydrobromide of formula (II) (54.2%) were obtained, having the melting point 135 to 139 °C. The crystals were characterized by an X-ray diffraction pattern (Figure 4) and infrared spectra as the crystalline Form II.

Example 3

6.88 g (0.02137 mol) of the clopidogrel base of formula (I) are dissolved in 100 ml toluene at room temperature. At this temperature, 2.25 ml of 48% HBr is added to the solution drop by drop. An oily matter precipitated out of the solution, which crystallized after 4 hours of stirring at room temperature. The resulting crystals were sucked off and washed with toluene. After air drying, 6.66 g of yellowish crystals of the hydrobromide of formula (II) (77.4%) were obtained, having the melting point 120 to 134 °C. The crystals were characterized by an X-ray diffraction pattern (Figure 3) and infrared spectra as the crystalline Form I (Figure 1).

The crystals provided the following X-ray diffraction pattern:

2θ [deg]	d [Å]	I	I/I0
10.65	9.64	71.07	16.65
11.53	8.90	66.64	15.61
14.70	6.99	250.69	58.73
16.30	6.31	103.94	24.35
18.70	5.50	227.88	53.39
19.56	5.27	92.56	21.68
21.12	4.88	113.71	26.64
22.11	4.66	63.85	14.96
23.06	4.47	96.56	22.62
23.52	4.39	422.71	99.03
24.08	4.29	256.23	60.03
25.26	4.09	108.85	25.50
25.79	4.01	426.86	100.00
26.18	3.95	61.00	14.29
27.40	3.78	150.10	35.16
28.39	3.65	196.78	46.10
28.90	3.58	116.94	27.40
29.86	3.47	90.02	21.09
30.94	3.35	154.84	36.27

32.73	3.17	337.56	79.08
33.37	3.12	287.31	67.31
36.33	2.87	73.66	17.26
36.76	2.84	98.37	23.05
37.71	2.77	147.66	34.59
39.12	2.67	120.60	28.25

Example 4

21.48 g (0.0667 mol) of the clopidogrel base of formula (I) were dissolved in 312 ml toluene at room temperature. The resulting solution is cooled down in a water-ice bath to temperature +5 °C. At this temperature, 7 ml of 48% HBr in toluene is added drop by drop within 10 minutes. The reaction mixture is then tempered to temperature 18 to 20 °C and stirred at this temperature for 3 hours. The resulting crystals are sucked off, washed with toluene and air dried at room temperature. 19.46 g of yellowish crystals of the hydrobromide of formula (II) (72.4%) are obtained, having the melting point 113-120 °C. The resulting crystals were characterized with an X-ray diffraction pattern and infrared spectra as the crystalline Form I.

Example 5

203 g of the clopidogrel base (0.6308 mol) were dissolved in 1000 ml of toluene. With stirring, the solution was cooled down to 0 to +5 °C. Introduction of gaseous hydrogen bromide into the cooled solution was started. The pressure bomb was positioned on a balance and after 50 g of hydrogen bromide has gone, the introduction was stopped; its total duration was ca. 15 mins. The temperature while adding hydrogen bromide ranged between +5 and +10 °C. The thick reaction mixture was then stirred at 0 to -5 °C for 4 hrs. The resulting crystalline matter was sucked off through a filter glass and washed with 500 ml of toluene. Air drying afforded 243.7 g of clopidogrel hydrobromide.

An X-ray analysis proved the Form II. HPLC purity more than 99.0 %.

Example 6

260.7 g of the clopidogrel base (0.8101 mol) were dissolved in 2600 ml of toluene. With stirring, the solution was cooled down to 0 to +5 °C. Introduction of gaseous hydrogen bromide into the cooled solution was started. The pressure bomb was positioned on a balance and after 65 g of hydrogen bromide has gone, the introduction was stopped; its total duration was ca. 15 mins. The temperature while adding hydrogen bromide ranged between +5 and +10 °C. The thick reaction mixture was then stirred at 0 to -5 °C for 4 hrs. The resulting crystalline matter was sucked off through a filter glass and washed with 500 ml of toluene. Air drying afforded 368.5 g of clopidogrel hydrobromide.

The resulting crystalline product was characterized by an X-ray diffraction pattern as new Form III. HPLC purity more than 99.5 %.

The resulting crystals provided the following X-ray diffraction pattern:

2θ [°]	d [Å]	I_{rel}
7.796	11.332	100.00
10.457	8.453	12.63
10.987	8.046	12.80
12.408	7.128	16.05
15.380	5.757	25.30
18.389	4.821	35.42
19.369	4.579	33.25
20.616	4.305	14.13
21.807	4.072	19.17
22.569	3.937	13.33
23.170	3.836	15.10
23.291	3.816	15.72
23.895	3.721	28.41
24.052	3.697	12.75
25.489	3.492	12.04
25.735	3.459	12.72

28.744	3.103	12.40

Example 7

Clopidogrel hydrobromide of Example 6 (368.5 g) was dissolved while stirring in 2000 ml of 2-propanol at a temperature up to 60 °C. To this solution methyl *tert*-butyl ether (MTBE) was added (2135 ml) at 45 to 55 °C. The solution was slowly cooled down to room temperature (ca. 2 hrs); crystallization started. After 2 hours, the solution was cooled down to 0 to -5 °C with stirring overnight (18 hrs). The precipitated crystals were sucked off and washed with 500 ml of MTBE.

91.2 % of theory of clopidogrel hydrobromide were obtained, which has been characterized by an X-ray diffraction pattern as Form II. HPLC purity more than 99.5 %.

Melting points were measured at Kofler's block. The diffraction pattern was obtained by means of X'PERT PRO MPD PANalytical diffractometer.